A Dissertation on

Assessment of Sentinel Lymph Node Using Methylene Blue Dye in

Carcinoma Breast

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BONAFIDE CERTIFICATE

This is to certify that **Dr. J. SAKTHIUSHADEVI,**bonafide student of M.Ch. Surgical Oncology (August 2012 to July 2015) in the Department of Surgical Oncology, Government Royapettah Hospital, Chennai – 600 014 has done this dissertation on "**Assessment of Sentinel Lymph Node Using Methylene Blue Dye in Carcinoma breast"** under my guidance and supervision in partial fulfilment of the regulations laid down by The Tamilnadu Dr. MGR. Medical University, Chennai for M.Ch. Surgical Oncology Examination to be held in August 2015.

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DECLARATION

I solemnly declare that the dissertation titled "**Assessment of Sentinel Lymph Node Using Methylene Blue Dye in Carcinoma breast**" was done by me at Department of Surgical Oncology, center for Oncology, Kilpauk medical college and Govt. Royapettah Hospital, Chennai between August 2012 to January 2015 under the guidance and supervision of Prof.R.Rajaraman. The Dissertation is submitted to The Tamil Nadu Dr.MGR Medical University towards the partial fulfillment for the award of M.Ch degree

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ABSTRACT

Title : Assessment of Sentinel Lymph Node Using Methylene Blue Dye in Carcinoma Breast

Key words :Breast cancer, sentinel node biopsy, methylene blue dye, axillary dissection

Management of axilla is an integral part of treatment of carcinoma breast. Axillary lymph node dissection has a well-established role in regional disease control and it provides information about the histopathological status which has significant prognostic and therapeutic implications. However only around 30 percent of the of clinically node negative patients prove to be histopathologically node positive which means that 70 percent of clinically node negative patients undergo axillary dissection and are exposed to its morbidities like neuropathies, seromas and upper extremity lymphedema. This can be avoided with a sentinel lymph node (SLN) biopsy. This study aimed to assess the feasibility of localization of the sentinel node with the blue dye alone and compare the nodal tumor positivity in relation to blue dye positivity . Thirty five patients with breast cancers with stages T1-T3, N0, and one patient with T3 N1 M0 disease who had become node negative post chemo therapy were included in the study.5 patients with breast cancer clinically node negative axilla were excluded from the study after they have found to have axillary nodes after ultrasound examination. Totally 36 patients were evaluated. This study demonstrates that sentinel node localization is possible with methylene blue dye alone with 88.88% localisation rate. Though limited by small sample size this study has shown a low false negative rate of 6.25%. which denotes that SLN biopsy using methylene blue dye alone is a highly reliable and predictable technique to stage the axilla in breast cancer patients. This technique may help to avoid complete axillary lymph node dissection in sentinel node negative patients thereby minimising the morbidity of axillary lymph node dissection.

Introduction:

Management of axilla is an integral part of treatment of carcinoma breast. Axillary lymph node dissection has a well-established role in regional disease control and it provides information about the histopathological status which has significant prognostic and therapeutic implications(1).However only around 30 percent of the of clinically node negative patients prove to be histopathologically node positive which means that 70 percent of clinically node negative patients undergo axillary dissection and are exposed to its morbidities like neuropathies, seromas and upper extremity lymphedema. This can be avoided with a sentinel lymph node (SLN) biopsy. Published data till date use vital blue dye and /or ^{99m}Technetium labelled colloid with gamma probe for the identification of sentinel lymph nodes. A combination of the two techniques has been found to be the best and is recommended for optimal outcome. Blue dye guided SLN identification may be the only available option in countries with low resources due to prohibitive price of gamma probes. This study was done to analyse methylene blue dye uptake after peri-tumoural injection and compare tumour positivity in nodes stained and unstained with blue dye in modified radical mastectomy specimens.

REVIEW OF LITERATURE

Addressing the axillary nodes is an integral component in the loco regional management of early breast cancer. A formal axillary lymph node dissection was until recently the standard procedure of choice for the management in the majority of the patients irrespective of primary tumour characteristics. Around 25-30% of patients have nodal disease at the time of diagnosis. For these patients removal of lymph nodes minimises the chance of loco regional relapse and can provide crucial information for guiding systemic adjuvant treatments. Moreover, axillary lymph node status remains the single most important prognostic factor in breast cancer (2). Nonetheless, for node negative patients axillary lymph node dissection represents over treatment and can be associated with significant morbidity. Sentinel node biopsy (SNB) permits accurate axillary staging of patients with early breast cancer with clinically node negative axilla. Sentinel node biopsy has less morbidity and fewer complications than axillary lymph node dissection (3).

Anatomy of the breast(4)

The adult female breast is located within the superficial fascia of the anterior chest wall. The base of the breast extends from the second rib above to the fifth or sixth rib below, and from the sternal border medially to the mid-axillary line laterally. Two-thirds of the base of the breast lies anterior to the pectoralis major muscle, the remainder lies over the serratus anterior muscle. A small part may lie over the aponeurosis of the external oblique muscle.

In about 95 percent of women there is a prolongation of the upper lateral quadrant toward the axilla. This tail (of Spence) of breast tissue enters a hiatus (of Langer) in the deep fascia of the medial axillary wall. This is the only breast tissue found normally beneath the deep fascia.

Skin

The epidermis of the areola and the nipple is distinguished from that of the surrounding skin by the colour imparted by blood vessels carried close to the surface in long dermal papillae. In females at puberty, and with each pregnancy, there is an increase in the melanin content of the basal cells, further darkening the area. The dermis of the skin merges with the superficial fascia, which envelops the parenchyma of the breast.

Superficial Fascia

The superficial fascia enveloping the breast is continuous with the superficial abdominal fascia (of Camper) below, and the superficial cervical fascia above. Anteriorly, it merges with the dermis of the skin.

Deep Fascia

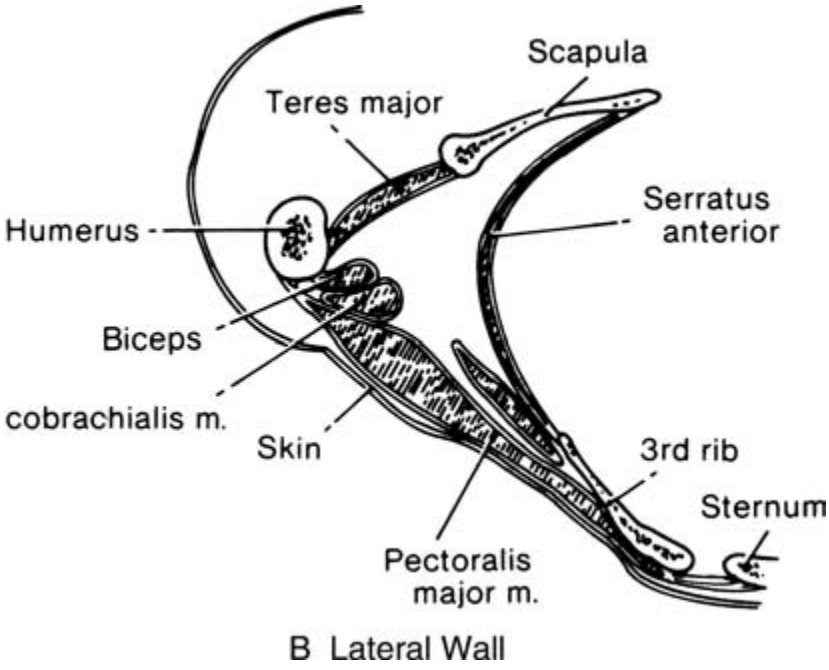
The deep pectoral fascia envelops the pectoralis major muscle and is continuous with the deep abdominal fascia below. It attaches to the sternum medially and to the clavicle and axillary fascia above and laterally. Along the lateral border of the pectoralis major muscle, the anterior lamina of the deep pectoral fascia unites with the fascia of the pectoralis minor muscle and, more

inferiorly, with the fascia of the serratus anterior. A posterior extension of this fascia is continuous with the fascia of the latissimus dorsi and forms the so-called suspensory ligament of the axilla.

Anatomy of the axilla

The axilla is defined as a pyramidal space having an apex, a base, and four walls. The apex is a triangular space bordered by the clavicle, the upper border of the scapula, and the first rib, which is sometimes called the cervico-axillary canal. The base consists of the axillary fascia beneath the skin of the axillary fossa. The anterior wall is composed of three muscles (the pectoralis major, the pectoralis minor, and the subclavius) and the clavipectoral fascia, which envelops the muscles and fills the spaces between them. The posterior wall is formed by the scapula and three muscles: the Subscapularis, the Latissimus dorsi, and the Teres major. The medial wall consists of the lateral chest wall, with the second to sixth ribs, and the serratus anterior muscle. The lateral wall is the narrowest of the walls, being formed by the bicipital groove of the humerus.The axilla contains lymph nodes, the axillary sheath, which covers blood vessels and nerves, and the tendons of the long and short heads of the biceps brachii muscle and the coracobrachialis muscle.

FIGURE-1 Lateral wall of the axilla



B Lateral Wall

Morphology of breast

Each breast is composed of between 15 and 20 lobes, some larger than others, within the superficial fascia, which is loosely connected with the deep fascia. Between the superficial and deep fascia is the retromammary (submammary) space, which is rich in lymphatics.Each lobe has a duct terminating at the nipple. These lobes, together with their ducts, are anatomical but not surgical units. In the fat-free area under the areola, the dilated portions of the lactiferous ducts (the lactiferous sinuses) are the only sites of actual milk storage. Intraductal papillomas may develop here. The suspensory ligaments of Cooper form a network of strong connective tissue fibres passing between the lobes of parenchyma and connecting the dermis of the skin with the deep layer of the superficial fascia.

Occasionally the superficial fascia is fixed to the skin in such a way that ideal subcutaneous total mastectomy is impossible. With malignant invasion, portions of the ligaments of Cooper may contract, producing a characteristic fixation and retraction or dimpling of the skin. This must not be confused with the retraction of '*peau d'orange'* secondary to lymphatic obstruction.

Vascular system of the breast

1. Thoracic Artery

The internal thoracic (or internal mammary) artery is a branch of the subclavian artery that parallels the lateral border of the sternum behind the internal intercostal muscles.

2. Branches of the Axillary Artery

Four branches of the axillary artery may supply the breast. They are, in order of appearance: (1) the supreme thoracic branch, (2) the pectoral branches of the thoracoacromial artery, (3) the lateral thoracic arteries, and (4) unnamed mammary branches.

3. Intercostal Arteries

The lateral half of the breast may also receive branches of the 3rd, 4th, and 5^{th}intercostal arteries.

Anatomy of the lymphatics(5)

The lymphatic system consists of a fluid (lymph), vessels that transport the lymph and organs that contain lymphoid tissue

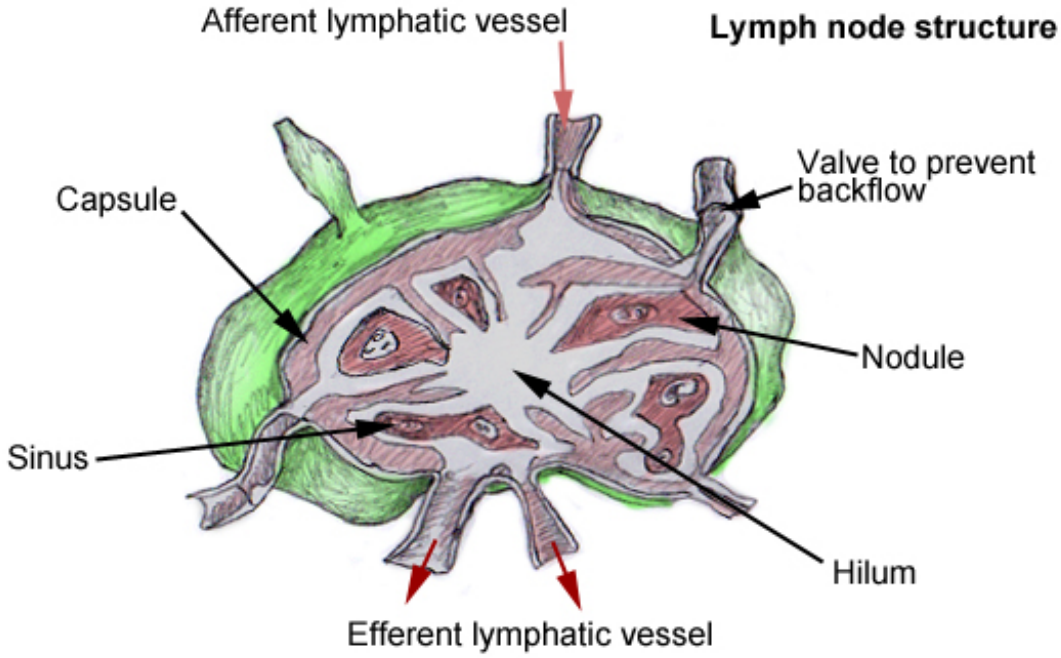
Lymph is a fluid similar in composition to blood plasma. It is derived from blood plasma as fluids pass through capillary walls at the arterial end. As the interstitial fluid begins to accumulate, it is picked up and removed by tiny lymphatic vessels and returned to the blood. As soon as the interstitial fluid enters the lymph capillaries, it is called lymph. Returning the fluid to the blood prevents edema and helps to maintain normal blood volume and pressure.

Lymphatic vessels carry fluid away from the tissues. The smallest lymphatic vessels are the lymph capillaries, which begin in the tissue spaces as blind-ended sacs. Lymph capillaries are found in all regions of the body except the bone marrow, central nervous system, and tissues that lack blood vessels (epidermis). The wall of the lymph capillary is composed of endothelium in which the simple squamous cells overlap to form a simple one-way valve. This arrangement permits fluid to enter the capillary but prevents lymph from leaving the vessel. The microscopic lymph capillaries merge to form lymphatic vessels. Small lymphatic vessels join to form larger tributaries, called lymphatic trunks, which drain large regions. Lymphatic trunks merge until the lymph enters the two lymphatic ducts namely the right lymphatic duct and the thoracic duct. The right lymphatic duct drains lymph from the upper right quadrant of the body. The thoracic duct drains all

the rest. Like veins, the lymphatic tributaries have thin walls and have valves to prevent backflow of blood. There is no pump in the lymphatic system like the heart in the cardiovascular system. The pressure gradients to move lymph through the vessels come from the skeletal muscle action, respiratory movement, and contraction of smooth muscle in vessel walls.

The lymphatic organs include lymph nodes, tonsil, spleen and thymus. Lymphatic organs are characterized by clusters of lymphocytes and other cells, such as macrophages, enmeshed in a framework of short, branching connective tissue fibres. Lymph nodes are small bean-shaped structures that are usually less than 2.5 cm in length. They are widely distributed throughout the body along the lymphatic pathways where they filter the lymph before it is returned to the blood. Lymph nodes are not present in the central nervous system. There are three superficial regions on each side of the body where lymph nodes tend to cluster. These areas are the inguinal nodes in the groin, the axillary nodes in the armpit, and the cervical nodes in the neck.

FIGURE-2 Lymph node structure



A typical lymph node is surrounded by a connective tissue capsule and is divided into compartments called lymph nodules. The lymph nodules are dense masses of lymphocytes and macrophages, separated by spaces called lymph sinuses. The afferent lymphatics enter the node at different parts of its periphery, which carry lymph into the node; entering the node on the convex side. The lymph moves through the lymph sinuses and enters an efferent lymphatic vessel, located at an indented region called the hilum, and carries the lymph away from the node.

Anatomy of the axillary lymph nodes

The lymphatic vessels of the upper limb, most of those from the breast, and cutaneous lymph vessels of the trunk above the level of umbilicus drain to the axillary lymph nodes. The primary route of lymphatic drainage of the breast is through the axillary lymph nodes. Unfortunately the boundaries for this group of lymph nodes found in the axilla are not well demarcated. Thus there has been considerable variation in the names given to lymph node groups.

Anatomical classification of axillary lymph node groups

1. LATERAL - Above the axillary vein, drain the upper limb

2. ANTERIOR - Along the inferior border of the pectoralis minor drain most of the breast

3. POSTERIOR - Subscapular nodes, drain the shoulder

4. CENTRAL - Near the base of the axilla receive lymph from the preceding three groups and form the most common palpable group.

5. APICAL – Lies medial to the axillary vein and superior to the pectoralis minor. Receive lymph from all the other groups sometimes directly from the breast. They drain into two or three subclavian trunks which enter the jugular-subclavian venous confluence or join a common lymphatic duct or empty into lower deep cervical nodes.

Surgical classification of axillary lymph node groups

1. Axillary vein group

2. External mammary group,

3. Scapular group,

4. Central group,

5. Subclavicular group,

6. Inter pectoral or Rotter s group

Surgeons also define the axillary lymph nodes with respect to their relationship with the pectoralis minor muscle.

Level I - Lymph nodes located lateral or below the lower border of the pectoralis minor muscle and include external mammary, scapular and axillary vein nodal groups

Level II- Lymph nodes deep or posterior to the pectoralis minor and include central and some of the subclavicular lymph node group

Level III - Lymph nodes medial or superior to the upper border of the pectoralis minor and include the subclavicular lymph node group.

Lymphatic system of the breast

The lymphatics of the breast form an extensive and complex network of periductal and perilobular vessels which drain principally to the axillary nodes. The lymphatic vessels occur in three interconnecting groups (6)

1. Primary set of channels within the gland

2. Sub areolar plexus

3. A plexus on the deep surface of the breast

Although the internal mammary nodes were recognized by Handley as a primary route for lymphatic drainage from medial and central zones of the breast(7), the majority of the breast cancer metastasise to the axillary nodes irrespective of the index quadrant(8). Fewer than 10% of the node positive tumours exclusively affect the internal mammary nodes (9). Accessory pathways of lymphatic drainage routes assume importance in more advanced states of disease when the axillary drainage routes become obstructed (10) and include the following routes,

1. Sub sternal crossover (contralateral internal mammary chain)(11)

2. Presternal cross over (contralateral breast)

3. Mediastinal (12)

4. Rectus abdominus sheath to sub diaphragmatic and sub peritoneal plexus.

Axillary lymph node dissection (ALND)

ALND refers to removal of lymph nodes in the axilla. A complete ALND refers to extirpation of the lymph nodes from all the three levels. A partial ALND refers to removal of lymph nodes from level I and level II, and Axillary sampling indicates only resection of level I nodes.

The axilla is a pyramidal space with an apex directed into the root of the neck; base bounded in front by the anterior axillary fold, which consists of the two pectoral muscles, the subclavius muscle and behind by the posterior axillary fold, formed by Teres major and Latissmus dorsi muscle and medially by the chest wall. The axillary tissue is composed of adipose tissue and lymph nodes.

Steps of axillary dissection

1. Definition of pectoralis muscles

The lateral edge of the pectoralis major muscle is retracted medially to expose the pectoralis minor muscle and allow interpectoral dissection of Rotter's lymph nodes.

2. Identification of Latissmus dorsi

The anterior surface of the Latissmus dorsi muscle is the lateral border of axillary dissection.

3. Clavipectoral fascia

The clavipectoral fascia is divided at the level of inferior axillary sheath to expose the underlying fat pad and axillary lymph nodes within the fat.

4. Axillary vein

Dissection is carried posteriorly until the axillary vein is exposed.(13)

5. Mobilization of axillary fat pad

The fatty tissue and lymph nodes cleared off the chest wall and the inferior surface the axillary vein.

6. Identification of nerves

The position of thoraco dorsal nerve and long thoracic nerve can vary from patient to patient. The best approach is to preserve all neuro vascular structures until full axillary anatomy can be determined. The thoraco dorsal neuro vascular pedicle can be identified by dissecting in the mid axilla. The long thoracic nerve can be identified by blunt dissection just below the medial aspect of the axillary vein and lateral to the chest wall.

Extent of dissection

In general level I and level II anatomic ALND is the preferred procedure for axillary assessment (14). Typical level I/II dissection should yield more than 10 axillary nodes.(15-16)

Routine removal of level III nodes is unnecessary and should be carried out to

maximize local control only if grossly positive lymph nodes are identified intra operatively at level I and level II. Level III lymph node dissection increases the morbidity of ALND (17).

Completion of ALND -Once the thoraco dorsal and long thoracic nerves are identified, contents of the axilla can be removed from the defined boundaries.

Methods of axillary node sampling

The recognition that axillary dissection was principally a staging procedure with concomitant morbidity led to investigation of alternative procedures for staging the axilla these included 1. Four node axillary sampling, 2.sentinel node biopsy

Four node axillary sampling

Axillary sampling was introduced more than two decades ago by Sir Patrick Forrest (18) the original technique of blind four node sampling of axilla could stage with estimated accuracy of 97%(19). This blind four node sampling is not associated with impaired loco regional control or any detriment in overall survival. (20) For patients found to be node positive on sampling, the axilla can be irradiated or surgically cleared (21)

Sentinel node biopsy

The sentinel node hypothesis presupposes an orderly spread of cancer cell to the sentinel node then to the higher echelon nodes. If the sentinel node is free from metastases, the non-sentinel nodes are presumed to be tumour free.

History of sentinel node concept

The concept of sentinel node biopsy is based on two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first echelon lymph node as an effective filter for tumour cells. With the wide spread use of sentinel node biopsy, sufficient data was needed to prove that sequential lymphatic dissemination and entrapment of tumour cells in first draining lymph nodes does occur.

The concept of selecting a single lymph node to represent a nodal basin is very old. In 1951 Gould sent a normal appearing node at the junction of anterior and posterior facial vein for frozen. Intraoperative examination of this lymph node in its typical anatomical location guided the decision to perform a radical neck dissection during the following parotidectomies (22).

Two decades later, Cabañas observed the existence of sentinel lymph node in carcinoma penis around the superficial epigastric vein in 1977 (23). These nodes were identified with lymphangiography. Kett et al administered contrast medium in breast lymphatics that were visualised with the aid of areolar blue dye injection (24). They observed flow to an isolated lymph node, called the ‘Sorgius’ node, and subsequent drainage through many lymphatic vessels and lymph nodes to the

collecting system around the axillary vein. Using breast lymphoscintigraphy in 1980, Christensen et al observed primary draining nodes [25]. Haagensen studied the route of metastases through the axillary lymph node and stated that the nodes of the central group are most often exclusively involved [26]. He used the term sentinel node for specific lymph nodes of the inferior deep cervical group.

Morton et al have used cutaneous lymphoscintigraphy with colloidal gold since 1977 to identify the lymphatic drainage pattern of melanomas located at ambiguous sites [27]. In addition to this preoperative procedure, they also developed a technique for intraoperative mapping to selectively remove lymph nodes on the direct drainage pathway from the primary melanoma. This sentinel node was considered to be the first site of metastatic disease. The work of the group at the John Wayne Cancer Institute initiated one of the most interesting recent developments in surgical oncology (28). Giuliano applied the concept of a negative lymph node to eliminate the need for radical dissection (29).

Indications and contraindications of axillary sentinel node biopsy in breast cancer

Clinical Indications of sentinel node biopsy have been changing and still there is debate on some of them. Sentinel node biopsy is indicated in most of the women with clinically node negative axilla with invasive or micro invasive breast cancer (30).Some of the current indications and recommendations are given below (31).

TABLE-1

Clinical scenario	Indication of sentinel node biopsy
T1 or T2 tumours	Established
Older age	Established
Obesity	Established
Before preoperative systemic	Established
Male breast cancer	Established
DCIS with mastectomy	Established
Internal mammary chain	Established but controversial
DCIS without mastectomy	Controversial
Pregnancy	Controversial
Suspicious, palpable axillary	Controversial
T3 or T4 tumours	Controversial
Multicentric or multifocal	Controversial
Prior diagnostic or excisional	Controversial
Prior axillary surgery	Controversial
Prior non-oncologic breast	Controversial
After preoperative systemic	Controversial
Inflammatory breast cancer	Not recommended

{DCIS - ductal carcinoma in situ; Controversial - indications suggest that the it is not universally accepted or the evidence behind the practice is limited.}

Contraindications

1.Prior axillary surgery

2.DCIS when lumpectomy is planned

3.Prior breast surgery

4. Pregnancy

5. Inflammatory breast cancer.

Role of ultrasound in sentinel node evaluation

For women with clinically suspicious axillary nodes, axillary ultrasound with fine needle aspiration or core needle biopsy provides a mean to identify the patients who have positive nodes and thus need ALND rather than the SLND.The efficacy of this approach is variable between centres because the accuracy of ultrasound examination is operator dependent (32)

Lymphatic mapping techniques for sentinel node biopsy

Given the rapid growth of lymphatic mapping and sentinel node biopsy surgical groups have developed several variations and many technical aspects are evolving which include

Choice of mapping label

Radio isotope quantity and processing

Injection site

Timing of injection

The use of preoperative lymphoscintigraphy.

Technique

Choice of mapping label

Radio isotope

Blue dye

Both radio isotope and blue dye

Radio isotope

Krag and colleagues first described the use of radioisotope alone for breast cancer in 1993, using technetium-99m sulphur colloid and a hand held gamma probe(33). The sentinel node identification rate was 98% with a false negative rate of 11%. Technetium-99 m sulphur colloid is the most commonly used isotope for lymphatic mapping in United States. In Europe technetium-99 m colloidal albumin is used. The dose range from -0.1 to 4 mCi

Blue dye

Isosulfan blue dye (Lymphazurin 1%) was studied extensively in melanoma. The use of Isosulfan blue dye as a single agent in sentinel node biopsy for carcinoma breast was reported by Giuliano and colleagues(34). The disadvantage is the risk of life threatening allergic and anaphylactic reactions. The reported allergic reactions rate ranges from 1% to 3%. They include utricaria,rash, pruritus, hypotension and anaphylaxis. Overall isosulfan blue dye has excellent results for lymphatic mapping in breast cancer most commonly used.

Methylene blue dye has also been successful in lymphatic mapping for breast cancer. Simmons et al used methylene blue in the identification of lymphatic mapping in breast cancer (35). Methylene blue was compared with Isosulfan blue by Blessing et al in 2002 and found similar identification rates (36).Methylene blue is preferred by some authors because of its lower cost and less complications. Methylene blue must be injected subcutaneously. Inadvertent injection into the dermis has resulted in severe skin reactions including necrosis and dermolysis.

Combination of blue dye and radioisotope

The combination of blue dye and radioisotope improves the sentinel node identification rate. Albertini et al first reported the successful use of lymphatic mapping with blue dye and radioisotopes prospectively (37).The results confirmed that the combination improves the sentinel node identification rate and dual agent lymphatic mapping has been accepted universally (38). Some centres have selected to rely on radioisotope mapping alone, given the potentially life-threatening allergic reactions of isosulfan blue dye.

Injection site for mapping agents

1. Peritumoural injection.

2. Subareolar and dermal injection.

Peritumoural injection

Peritumoural injection replicates the intramammary lymphatic pathway that has been traversed by metastases. The initial data regarding sentinel node biopsy used peritumoural injection. For patients who have nonpalpable tumours this method has proven to be difficult and time consuming as it requires the use of additional imaging modalities to guide the Peri-tumoural injection of radioisotopes. Peri-tumoural injections also have a higher potential for shine through where residual radioactivity from the peri-tumoural injection site creates misleading background activity detected by the gamma probe in the axilla. It is for these reasons that alternate injection sites have been tried.

Subareolar and dermal injection

Nearly all breast tissue lymphatics pass through the sub areolar plexus of Sappey and then to the axillary basin. Non palpable and multicentric tumours can be studied with sub areolar and dermal injection and they do not have the shine through effect. Sub areolar and dermal injection of blue dye may cause considerable skin discoloration which may last for months. In addition up to 10% of breast cancers may demonstrate non axillary lymphatic drainage with sentinel nodes found in the internal mammary or supraclavicular nodal basins; so, not all breast tumours will have the same drainage patterns as the overlying skin and nipple areas (39).

Preoperative lymphoscintigraphy

Patients undergoing lymphatic mapping with radioisotopes most often receive a

pre-operative lymphoscintigram,to aid in sentinel lymph node (SLN) identification.

Pre-operative lymphoscintigram, consists of anterior and lateral view and specific patient positioning to optimize transit time and drainage (40). Scanning is done after 20 minutes and images are repeated till identification of SLN basin then the patient is taken to the operating room for SLNB..McMasters and colleagues (41) evaluated the role of pre-operative lymphoscintigram, in breast cancer. In the study, a pre-operative lymphoscintigram, was performed in 348 of 588 patients, and 240 patients did not receive scans. The SLN was identified in 221 of the 240 patients who did not undergo preoperative scanning. In these patients, the false-negative rate was 1.6%. The authors found no significant difference in the SLN identification rate, false-negative rate, or number of SLNs removed between patients receiving PL and those proceeding to operation without scanning.

Borgstein and colleagues(42) also studied the role of PL in breast cancer patients. The authors found that the intraoperative gamma probe was more sensitive in detecting radioactive nodes in the axilla than the PL, even when delayed images were obtained. Data have continued to emerge questioning the ability of preoperative lymphoscintigraphy to improve the accuracy of SLNB and

some centres have abandoned the technique, relying on the intra operative gamma probe to detect radioactive SLNs.

Timing of radio isotope injection

Lymphatic mapping with radio isotopes is performed either as a 1 or 2 day procedure.(43) The single day procedure requires isotope injection on the morning of surgery followed by serial imaging 1 to several hours after injection until the SLN is identified. The effect of delay on patients and on operating room has led to use a 2 day mapping procedure, with injection of radio isotopes 1 day before operation. Based on the current literature, 2 day lymphatic mapping procedure is safe and reliable method of SLN identification.(44)

Technique

Blue dye

The patient is prepped and draped in the operating room. The surgeon injects 3-5ml of blue dye peritumourally or sub dermally

The axillary fascia is entered through an inferior axillary incision. Careful search is made for lymphatic channels leading to blue stained node. All blue nodes and nodes at the end of the blue lymphatic channel are removed .Care must be taken to identify the most blue node and the blue node most proximal to the tumour in the axilla , because the dye transit time is rapid and blue staining of distal, non-sentinel axillary LNs is not uncommon. Failure to consider the node at the end of

blue lymphatic channel as a sentinel node whether or not the node itself appears blue is the most common technical error (45).

Radioactive colloid (46)

Technetium-99m-labeled colloids with a particle size of 20 –100 nm and an injection volume of 0.2–1.0 mL generally are used. The amount of radioactivity has to be determined according to the time between radio-colloid injection and the surgical procedure to obtain a sufficient radio-colloid uptake in the lymph node and a high target signal intensity.

If surgery is planned 24 hours after the injection and a probe with a sensitivity of 10 cps/kBq is used, then activity of 150 –250 megabecquerel (MBq) will be needed. With a nuclide half-life of 6 hours (Technetium-99) and an injection time 6 hours prior to SLNB, the amount of radioactivity required is reduced by 50%. In 1-day protocols, 10 –50 MBq are sufficient. Tracers may be injected into the peritumoural tissue, intratumourally, intradermally or in the subareolar region. The patient lies supine for imaging on the gamma-camera bed 3hours after the injection of tracer .Anterior and 45° anterior oblique static scintigraphic images are obtained by using a dual head gamma camera with low energy high resolution collimator. The site of any suspected sentinel node can be

localised on overlying skin on the 45° anterior oblique image and the skin of the patient on the identical site marked with a small spot of indelible ink.

The first “hot spot” detected on images has to be considered as the sentinel lymph node. During the operation, the surgeon guided by the skin mark will locate the lymph node with the highest radioactivity, with the hand held gamma probe. All nodes with radioactive counts more than 10 times the back ground count,as measured in the ante cubital fossa using hand held gamma probe are identified as sentinel nodes.(47). If there are two or more such lymph nodes, all should be removed. Before sending for histological examination, any lymph node removed should be re-checked by the probe to demonstrate that they are radioactive.(48)

The disadvantages of SLNB

1. Skip metastasis alter management predictions.
2. Learning curve
3. Radionuclide retention in tissues.
4. Failure to identify sentinel nodes

Pathological evaluation of SLNs

Pathological assessment of the SLN is done both intra operatively and post operatively. Intraoperative assessment permits axillary surgery in a single session if the SLN is positive intraoperatively or truly negative on the definite histopathologic

evaluation. The postoperative examination provides the final histopathologic status of the SLN for the definitive decision to be taken for further loco regional and systemic treatment.

Intra operative evaluation

Intra operative examination, at the beginning of SLN era was done only to evaluate the nodal tissue, because the tissue removed may not represent true lymph node .Intra operative evaluation is used only if it influences immediate management. Both frozen sections and imprint have been very efficient in detecting metastases intra operatively (50)

Frozen section

Each SLN is grossly sectioned at 0.2 cm interval portions. The most superficial 25% of the thickness of each resulting 0.2 cm SLN tissue section is processed for frozen section analysis, providing at least three separate levels of tissue for frozen section analysis. These frozen sections are then hand-stained by routine Hematoxylin and Eosin (H&E) staining. The remaining tissue of each resulting 0.2 cm SLN tissue section, encompassing 75% of the thickness of that tissue, is then sent for routine processing. (51)

Imprint cytology

Excised lymph nodes submitted for intraoperative evaluation are examined using one of 2 methods depending on which institution is performing the

evaluation. In the first method, the SLN is bisected along the long axis. Care is taken to obtain complete cross sections of the maximum diameter, preferably including the hilum and the marginal sinus. For each lymph node half, a pair of imprints is made by gently touching the cut surface of the SLN to a glass slide. One imprint from each pair is air dried and stained with the Diff-Quik stain. The second imprint from each surface is immediately fixed in 95% ethanol for 3 minutes and then stained with hematoxylin and eosin (H&E). In the second method, the SLN is sliced into 4-mm slices and imprints are made of each cut surface, air-dried, and stained with Diff-Quik(52)

Post-operative examination

The extent and meticulousness of the histopathologic work-up of SLNs should depend on the relevance of the results for further treatment decisions. The prognostic significance of micrometastasis, their predictive role for the involvement of non-SLNs, and the clinical consequences of a false-negative staging due to undetected micrometastasis still are being debated. However, the clinical implications of micrometastatic involvement of SLNs do not justify a systematic search for all micrometastasis. There is no doubt that all macrometastasis should be detected during the definitive pathologic examination.

1embedding of the lymph node and a homogeneous distribution of the levels histologically examined. This can be achieved by producing SLN slices of 3 mm thickness for the macroscopic examination and for step sectioning. In instances of

negative macroscopic findings, the slices should be examined at regular, 500um intervals (maximum, 6 steps). This approach provides a theoretical detection rate for macrometastasis of 100% (53).

Immune histochemistry (IHC)

The use of cytokeratin may facilitate pathological finding. The use of immunohistochemistry in the evaluation of SLNs is controversial. If the aim is to correctly stage the disease with the exclusion of micrometastasis then the IHC should be used.

Molecular pathology

Molecular methods using reverse transcriptase polymerase chain reaction have been used to detect the tumour cell. Reverse transcriptase-polymerase chain reaction analysis is a highly sensitive method. However, it is difficult to find a RNA sequence that is specific for single tumours. Hence, it may be necessary to use a panel of markers. High sensitivity, however, is associated with the risk of false-positive result

Results from the American College Of Surgeons Oncology (ACOSOG)study Z0010,confirm that IHC detected metastases have no impact on

overall survival.(54) Thus routine IHC or PCR is not recommended for the valuation of SLNs in guidelines published by ASCO 2014,NCCN 3.2014 and others.(55)

Documentation of histopathological findings

SLNB requires standardized documentation of the histologic findings. Every SLN must be sent separately for histopathologic examination with a specific identification number. The location and sequence of removal and the method of detection (including target count)should be documented by the surgeon. The histopathologic results are reported as the pathologic lymph node (pN) category according to the UICC TNM classification system7th edition

STAGING OF CARCINOMA BREAST

International Union Against Cancer (UICC) TNM classification system and by the American Joint Committee on Cancer(AJCC) 7th edition

TABLE-3

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis(DC	Ductal carcinoma in situ
Tis(LC	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumour ≤ 20 mm in greatest dimension
T1mi	Tumour ≤ 1 mm in greatest dimension
T1a	Tumour> 1 mm but ≤ 5 mm in greatest dimension
T1b	Tumour> 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumour> 10 mm but ≤ 20 mm in greatest dimension
T2	Tumour> 20 mm but ≤ 50 mm in greatest dimension
T3	Tumour> 50 mm in greatest dimension

T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peaud'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures

N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s),
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

*"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis on the basis of fine-needle aspiration (FNA) biopsy with cytologic examination.

Pathologic (pN)*

Pnx	Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)

pN0	No regional lymph node metastasis identified histologically. *Note:* Isolated tumour cell clusters (ITCs) are defined as small clusters of cells ≤ 0.2 mm, or single tumour cells, or a cluster of < 200 cells in a single histologic cross-section; ITCs may be detected by routine histology or by immunohistochemical (IHC) methods; nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated
pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) ≤ 0.2 mm (detected by haematoxylin-eosin [H&E] stain or IHC, including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
pN0(mol+)	Positive molecular findings (RT-PCR) but no regional lymph node metastases detected by histology or IHC
pN1	Micro metastases; or metastases in 1-3 axillary lymph nodes and/or in internal mammary nodes, with metastases detected by sentinel lymph node biopsy but not clinically detected†

pN1mi	Micro metastases (> 0.2 mm and/or > 200 cells, but none > 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes (at least 1 metastasis > 2.0 mm)
pN1b	Metastases in internal mammary nodes, with micro metastases or macro metastases detected by sentinel lymph node biopsy but not clinically detected†
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†
pN2	Metastases in 4-9 axillary lymph nodes or in clinically detected‡ internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least 1 tumour deposit > 2.0 mm)
pN2b	Metastases in clinically detected‡ internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥ 10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected‡ ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive level I, II axillary lymph nodes; or in > 3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but

	not clinically detected†; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥ 10 axillary lymph nodes (at least 1 tumour deposit > 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected‡ ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive axillary lymph nodes; or in > 3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected†
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
*Classification is based on axillary lymph node dissection, with or without sentinel lymph	
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastasis
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow, or other non regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven > 0.2 mm

TABLE-4

Generic TNM Coding For Sentinel Nodes	
pNX (sn)	Sentinel lymph node could not be assessed
pN0 (sn)	No sentinel node metastasis
pN1 (sn)	Sentinel node metastasis
Sentinel nodes with micrometastasis only are identified by (mi)	
pN1(sn) (mi)	Single ipsilateral node with micrometastasis
pN2 (sn) (mi)	Multiple ipsilateral nodes with micrometastasis.
Sentinel nodes with isolated tumour cells	
pN0 (i-)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for isolated tumour cells (ITC)
pN0 (i?)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for isolated tumour cells (ITC)
pN0 (mol-)(sn)	No sentinel lymph node metastasis histologically, negative non-morphological findings for isolated tumour cells (ITC)
pN0 mol?)(sn)	No sentinel lymph node metastasis histologically, positive non-morphological findings for isolated tumour cells (ITC

Management of positive sentinel node.

Isolated tumour cells

The seventh edition of the American Joint Committee on Cancer (AJCC) tumour node metastasis (TNM) staging system for breast cancer includes a stringent classification for lymph node findings of isolated tumour cell clusters and

single cells. Small clusters of cells not greater than 0.2 mm, or non-confluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section, are classified as isolated tumour cells and are considered prognostically similar to node negative patients.

Malignant cells in regional lymph node(s) no greater than 0.2 mm are designated as pN0(i+). Isolated tumour cells are not considered an indication for further axillary surgery, radiation treatment, or adjuvant systemic therapy. The finding of isolated tumour cells in lymphatics as a result of iatrogenic displacement from core biopsy procedures has been observed and is not considered to be clinically significant.(56-57)

Micrometastases — SLND allows the pathologist to perform a more detailed study of few lymph nodes that most likely contain metastases this has the potential to improve the staging accuracy, but with increase in the rate of identification of micro metastatic nodal involvement(58). For this reason, there is a separate designation of pN1mi (>0.2 mm and no greater than 2.0 mm) to indicate the micrometastasis alone.

Although patients with micrometastasis are considered node positive, this finding does not change the survival compared with those without micrometastasis.(59).However some analyses suggest a negative impact of micro metastases on outcomes including regional recurrence rate. Pathological evaluation for occult metastases in a randomised trial of patients who underwent SLND alone

or SLND plus ALND for invasive breast cancer detected occult metastases in 16% of patients (60).

In the management of positive SLN nodes, there is general acceptance of the following approaches.

Patients with SLN showing isolated tumour cells are considered node negative and completion ALND is not indicated (61)

In patients with a positive SLN showing micrometastasis or macrometastasis in three or more nodes detected with standard hematoxylin & eosin examination , completion ALND is indicated(62). The timing of the procedure immediate versus delayed does not seem to affect the total lymph node yield or the rate of long term complications(63)

Completion ALND in patients showing micrometastasis or macrometastasis in less than three nodes may not be necessary because the SLN is the sole tumour-bearing node in up to 60 percent of cases overall, and in almost 90 percent of patients who harbour only micrometastatic disease. These observations have led to speculation that completion ALND may not be necessary in selected patients with a positive SLND in less than three nodes because the need for systemic therapy is established (64) and the risk of an axillary recurrence appears to be low(65-66).

A retrospective review of studies including randomized and prospective trials with at least two years follow up supports a completion ALND in select group of patients with following criteria(67)

1. Palpable or needle proven axillary metastases

2. SLN positive undergoing mastectomy without radiation therapy

3. Three or more SLN positive

Important trials and current guidelines in the management of SLN positive patients.

1. ACOSOG Z –0010

A multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer

Patients underwent breast conservation surgery and SNB with bilateral iliac crest BM aspiration. BM and histologically negative SN were evaluated with IHC.

This study evaluated prognostic significance of metastases detected in bone marrow by IHC and metastases detected in SLN by routine histopathology and IHC

In multivariate analysis there was no difference in Overall survival (OS), disease-free survival, and loco regional recurrence in patients tested negative for metastases in SLN by both IHC& histopathology and positive for metastases by IHC.

In a subset analysis it was seen that there was no significant difference in the rate of sentinel node identification with the use of blue dye alone or radio colloid alone or the combination of the two

This study, questions the routine examination of SN by IHC.(68)

2.ACOSOG Z –0011

This study was designed to address the need for completion ALND for patient with less than three SLN positive. All were treated with breast conservation surgery and whole breast radiation therapy (69).Women with clinically T1, T2, N0 and a positive sentinel node were randomly assigned into two arms, ALND versus No ALND. Primary end point was Overall Survival (OS) and secondary end points were axillary recurrence and surgical morbidities

The results of the trial included, at a median follow-up of 6.3 years, no significant differences in survival or loco regional recurrence between the SLND with ALND group versus the SLND alone group. The five-year overall survival was similar whether women were treated with SLND plus ALND or with SLND alone (91.9 versus 92.5 percent, respectively) (HR 0.79, 90% CI 0.56-1.10).The five-year disease-free survival was also similar between the two arms (82.2 versus 83.9 percent, respectively).Recurrence rates in the ipsilateral axilla were similar between the two arms with four recurrences (0.9 percent) in the SLND alone arm compared with two recurrences (0.5 percent) in the SLND plus ALND arm.

Women in the ALND group had a significantly greater incidence of postoperative complications than did the SLN-only group (70% vs25%).

The ACOSOG Z-0011 trial was criticized for a number of performance deficiencies; including target accrual for ACOSOG Z-0011 study was 1900 patients. The study closed prematurely because of low accrual and low event rate after enrolling 436 patients in the SLND alone arm and 420 in the SLND plus ALND arm. The trial was not adequately powered to meet the predetermined statistical survival primary endpoint due to low accrual. Eleven patients assigned to the SLND only arm did have an ALND and 32 patients assigned to the SLND plus ALND arm did not have an ALND. Almost 20 percent of patients were lost to follow-up and 7 percent of patients in the SLND arm were found to be node negative compared with 1 percent of the ALND arm. There was no breakdown of the numbers of patients with isolated tumour cell clusters, micrometastasis or macrometastasis in the two arms. The majority of patients had T1 (almost 70 percent), hormone receptor positive tumours (85 percent). Estrogen receptor status and adjuvant systemic therapy were independent predictors of survival.

Based upon the apparent lack of regional benefit and low risk of events in this trial, completion ALND may not be necessary for all women with T1 tumours that are clinically node negative, treated with breast conservation surgery ,with less than three positive SLNs, who will be treated with whole breast radiation, particularly in women with estrogen receptor positive tumours.

This was also shown in a retrospective review of 242 consecutive patients who met the ACOSOG Z0011 criteria (70).

When completion ALND is omitted in patients with a positive SLND, whole breast radiotherapy is indicated. If partial breast radiation is planned, completion ALND should be performed.

3. IBCSG 2301 trial- the international Breast Cancer Study group trial 2301

This trial analysed in patients with micro metastases in SLNs -ALND vs. No ALND

Patients with SLN micrometastasis (<2 mm) and primary tumours <5 cm in size were randomized to completion for ALND Vs. no additional axillary surgery (71). The primary end-points were five-year disease-free survival (DFS) and overall survival (OS) rates.

The results of the trial showed that with a median follow-up of 49 months, there was no significant difference in DFS rate for patients treated with an ALND compared with those treated with a SLND (87 versus 92 percent).There was no significant difference in OS rate for patients treated with an ALND compared with those treated with a SLND (97.6 versus 98.0 percent).The results of this trial, when considered in the context of the ACOSOG Z0011 trial, offer *additional support to the concept that a subset of patients with metastases to sentinel nodes may in fact*

do well with SLND alone as compared with a completion ALND. However, the data are derived from studies that are underpowered and have relatively short follow-up.

3. AMAROS trial(After Mapping of the Axilla: Radiotherapy Or Surgery)

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023AMAROS) (72) was studied

Patients were randomly assigned (1:1) by a computer-generated allocation schedule to receive either axillary lymph node dissection or axillary radiotherapy in case of a positive sentinel node, stratified by institution. The primary end point was non-inferiority of 5-year axillary recurrence, considered to be not more than 4% for the axillary radiotherapy group compared with an expected 2% in the axillary lymph node dissection group.

5-year axillary recurrence was 0·43% (95% CI 0·00-0·92) after axillary lymph node dissection versus 1·19% (0·31-2·08) after axillary radiotherapy. The planned non-inferiority test was underpowered because of the low number of events. Lymphoedema in the ipsilateral arm was noted significantly more often after axillary lymph node dissection than after axillary radiotherapy at 1 year, 3 years, and 5 years.

Results prove Axillary lymph node dissection and axillary radiotherapy after a positive sentinel node provide excellent and comparable axillary control for patients with T1-2 primary breast cancer and no palpable lymphadenopathy. Axillary radiotherapy results in significantly less morbidity.

4. NCCN guidelines version 3.2014– recommendation

ALND may be avoided in patients who have positive SLN provided all the following criteria are met

1. T1 or T2 tumours

2. 1 or 2 positive sentinel nodes

3. No neo adjuvant chemo therapy

4. Breast conservation therapy

5. Whole breast Radiation Therapy is planned

ALND should be performed even if one of the above criteria is not met

ASCO guidelines 2014(73)

In patient with less than three SLN positive node, completion ALND need not be performed, provided there is no evidence of bulky metastatic disease, gross extra capsular extension and the patient is treated with whole breast irradiation.

Complications of axillary lymph node dissection

1.Seroma

2.Arm morbidity

3. Infection

4. Hematoma

5. Nerve injury

1. Seroma – The normal lymphatic drainage of the breast to the axilla can lead to seroma formation after axillary dissection (78, 79). Seromas can be diminished with the use of drains or managed via percutaneous aspiration

2. Arm morbidity – Lymphedema of the arm is a potential and serious complication of ALND. The rate varies substantially with the level of dissection and whether or not postoperative radiation therapy is used. Shoulder stiffness, and numbness and paresthesias in the upper arm are common complaints following an ALND. Although these symptoms do not usually interfere with daily living, they may reduce the quality of life (80, 81).

3. Infection – The incidence of postoperative wound infection following axillary dissection varies from 3 to 15 percent in the literature (77).The most common organisms are usually gram positive (streptococcal or staphylococcal species) and will respond to treatment with appropriate oral antibiotics. If there is an underlying seroma, it should be aspirated and cultured to direct antibiotic treatment.

4.Hematoma – The reported incidence of postoperative hematoma has varied from 2 to 10 percent

5. Nerve injury- The risk of major motor nerve injury following an ALND is <1 percent. Injury to the long thoracic nerve results in a winged scapula. Injury to the thoracodorsal nerve weakens shoulder abduction and internal rotation. Injury to the medial pectoral nerve may lead to atrophy of the lateral aspect of the pectoralis major muscle, which may impact the overall cosmetic result. Transection

of the intercostobrachial nerve results in numbness and paresthesias on the inner upper arm.

Complications of sentinel node biopsy

1. Axillary paresthesia- 8.6%
2. Seroma-7.1%
3. Lymphedema-6.9%
4. Decreased range of motion-3.8%
5. Hematoma-1.4%
6. Axillary wound infection-1%
7. Axillary web syndrome.

Axillary paraesthesia was found in 8.6% presumably due to damage to the inter-costobrachial nerve. Decreased range of motion was reported in 3.8% and lymphedema in 6.9 %.(74) Axillary web syndrome is the development of palpable tender cords in the axilla antecubital fossa or upper arm It occurs after SNB but less commonly than ALND. The pathogenesis proposed by research groups is lymphovenous damage, hyper coagulation, superficial venous and lymphatic stasis as well as disorders and injuries of tissues as a result of the disruption of superficial lymphatics and vessels during axillary surgery. The condition can be treated by physiotherapy and massage (75).

SLNB is associated with significantly less subjective and objective long-term morbidity than ALND((82). The risk of lymphedema reported with SLN

biopsy is 2% to7% compared with a lifetime risk of lymphedema with ALND of 25%.Lucci et al12 compared the postoperative complication rate of women undergoing SLN vs. SLN and ALND in the ACOSOG Z0011study. They found that women in the ALND group had a significantly greater incidence of postoperative complications than did the SLN-only group (70% vs. 25%). Complications included wound infection, axillary seromas, axillary paresthesias, brachial plexus injury, and lymphedema. As reported subjectively by study participants, the development of lymphedema was 13% at 1 year in the ALND group vs. 2% in the SLN-only group.

Axillary recurrence after SNB

Axillary recurrence is rare after negative sentinel node biopsy. In 2000 Giuiliano and colleagues published the first prospective report of patients with negative SLNs being treated without ALND After surgery, all decisions regarding systemic adjuvant treatment and radiotherapy were based on conventional criteria. . With a median follow up of 39 months there was no axillary recurrence (83). Naik and colleagues (84) studied patients who underwent SNB and found axillary recurrence rate 1.4% the rate of recurrence was higher in patients who had positive SLNs and did not undergo ALND .Axillary recurrence can be treated with ALND(85) .

False negative rates of SLN biopsy

The false rates of SLN biopsy has been reported to be 6.7%to 9.7% .A false negative rate may increase the risk of axillary recurrence .In the NSABP-32 trial, the site of the tumour, the type of biopsy, and the number of SLNs removed all affected the false negative rate. Studies have confirmed that combination of blue dye and radio colloid has the highest sentinel node identification rate and the lowest false negative rate (86). A previous excisional biopsy has the potential to increase the false negative rate, as the dye or radioactive material may enter the seroma cavity.

Special considerations

Sentinel node biopsy in prophylactic mastectomy

Some surgeons perform SNB for prophylactic mastectomy because of the possibility of finding an occult carcinoma in the breast upon pathological evaluation. If invasive carcinoma is found after the surgery SNB is no longer possible and ALND should be performed. King &Colleagues studied the use of SNB in prophylactic mastectomy. Occult carcinoma was found in 8.0 %. DuPont&Colleagues also published a series of patients with 3.5% occult carcinoma in prophylactic mastectomy(87). Another consideration is in the event of immediate reconstruction ALND may alter the cosmetic appearance or may compromise the vascularity of the flap. These complications can be avoided with SNB.

Sentinel node biopsy in ductal carcinoma in situ (DCIS)

Patients with Ductal carcinoma in situ, who undergo breast conservation surgery do not require axillary staging, however women with DCIS may be candidates for SLN biopsy if they are undergoing mastectomy. Since it would be essentially impossible to perform an SNB subsequently if invasive cancer is found in the specimen which would necessitate an ALND. Axillary surgery would be problematic even more if immediate reconstruction was completed with free flaps or flaps with Trans-axillary pedicles. For these reasons SNB is indicated for patients undergoing mastectomy for DCIS.

Sentinel node biopsy and large tumours

Most of the initial trials with SNB were for small tumours .Chung and Colleagues(88) performed SNB in tumours >5cm size .SNB accurately predicted the nodal status with false negative rate of 3%. Large tumours have high incidence of axillary metastases but with clinically node negative axilla, SNB may be performed

Sentinel node biopsy after neoadjuvant chemotherapy

Sentinel lymph node biopsy after neoadjuvant chemotherapy in clinically node positive breast cancer at initial presentation has been studied in many series. In NSAPB B-27(89),a neoadjuvant trial requiring ALND ,some surgeons attempted SNB before the required ALND. The overall success rate in sentinel node identification was only 84.8% after neoadjuvant chemotherapy,with false negative rate of 10.7%.There were no significant differences in false negative rate that were

associated with tumour characteristics lymphatic mapping method (blue dye ,radioisotope or both) or the response to chemotherapy. The optimal timing of sentinel node biopsy in patients receiving neoadjuvant therapy has been debated as some have reported a higher false negative rate for SLND performed after induction therapy while others not(90).

The SENTINA (**SENTI**nel**N**eo**A**djuvant) study (91) was designed to evaluate a specific algorithm for timing of a standardised sentinel-lymph-node biopsy procedure in patients who undergo neoadjuvant chemotherapy. SENTINA was a four-arm, prospective, multicentre cohort study undertaken at 103 institutions in Germany and Austria.Women with breast cancer who were scheduled for neoadjuvant chemotherapy were enrolled into the study. There were four arms in the study

1.Patients with clinically node-negative disease (cN0) underwent sentinel-lymph-node biopsy before neoadjuvant chemotherapy (arm A).

2. If the sentinel node was positive (pN1), a second sentinel-lymph-node biopsy procedure was done after neoadjuvant chemotherapy (arm B).

3. Women with clinically node-positive disease (cN+) received neoadjuvant chemotherapy. Those who converted to clinically node-negative disease after chemotherapy (ycN0; arm C) were treated with sentinel-lymph-node biopsy and axillary dissection.

4. Only patients whose clinical nodal status remained positive (ycN1) underwent axillary dissection without sentinel-lymph-node biopsy (arm D).

The primary endpoint was accuracy (false-negative rate) of sentinel-lymph-node biopsy after neoadjuvant chemotherapy for patients who converted from cN1 to ycN0 disease during neoadjuvant chemotherapy (arm C). Secondary endpoints included comparison of the detection rate of sentinel-lymph-node biopsy before and after neoadjuvant chemotherapy, and also the false-negative rate and detection rate of sentinel-lymph-node biopsy after removal of the sentinel lymph node. Analyses were done according to treatment received (per protocol).

The false-negative rate and detection rate of sentinel-lymph-node biopsy after

removal of the sentinel lymph node. Analyses were done according to treatment received (per protocol).

Results of the study of SENTINA trial include, sentinel-lymph-node biopsy is a reliable diagnostic method before neo adjuvant chemotherapy. After systemic treatment , the procedure has a lower detection rate and a higher false-negative rate compared with sentinel-lymph-node biopsy done before neo adjuvant chemotherapy. These limitations should be considered if biopsy is planned after neo adjuvant chemotherapy.

The 3.2014 NCCN guidelines recommend that SLND be performed prior to neoadjuvant chemotherapy as it provides valuable prognostic information for planning loco regional treatment (92)

ACOSOG Z 1071 found a 12.6% false negative rate in when SLB performed post neoadjuvant chemotherapy (93). This limits the use of the procedure until further refinement either in the technique or patient selection.

In 2014 ASCO guidelines indicate that there is insufficient data at present to support the use of sentinel node biopsy after the neo adjuvant chemotherapy given the high false negative rates in the published trials (94)

Sentinel node biopsy in clinically node positive axilla

Most of the studies in the SLN biopsy have excluded clinically suspicious axillary nodes. It is well known that determination of the axillary lymph node status by clinical examination alone is unreliable with positive predictive value(PPV) of 64%-82% and a negative predictive value (NPV) of 50%-63% with overall accuracy of 63%-68%.(95)Specht&colleagues published a review of SNB in patients with clinically suspicious axillary nodes(96) and concluded that the clinical axillary examination in breast cancer is subject to false-positive results, and is by itself insufficient justification for axillary lymph node dissection.

If other means of preoperative assessment such as palpation- or image-guided fine needle aspiration are negative or indeterminate, then SLN biopsy

deserves wider consideration as an alternative to routine axillary lymph node dissection in the clinically node-positive setting. NCCN 3.2014 guidelines recommend FNA of the clinically suspicious axillary node and if it is negative then SNB can be done.

Sentinel node biopsy in male breast cancer

The vast majority of published studies of SLB for breast cancer are in women since the male breast cancer is uncommon. A retrospective study of 30 men with breast cancer reported a 100 per cent identification rate (97). Prospective studies are yet to be carried out. The principles that apply for SLB in female breast cancer appear to apply in male breast cancer.ASCO guidelines2014 acknowledges that there is limited data to support the use of SNB in men but there are no compelling reasons it should not be successful.

Sentinel node biopsy in pregnancy

Pregnancy associate breast cancers tend to present at a later stage and be estrogen receptor negative. The safety of SNB in pregnancy has not been established. Vital dyes such as Isosulfan blue dye should not be administered due to lack of safety. Methylene blue dye and 99m Technetium can be safely administered. A retrospective study by Gropper et al (98) that included 25

clinically node negative pregnant patients who were administered methylene blue (n = 7) or 99-Tc (n = 16), and two with unknown injection material, found at 2.5 years of follow-up no adverse fetal outcomes that could be attributed to the injection. Injections were performed at various trimesters. There were 25 livebirth infants, 24 of whom were deemed healthy at delivery; one infant had a cleft lip not attributed to the injection.

.NCCN 3.2104 guidelines conclude that radio colloid is safe during pregnancy.

2014 ASCO guidelines recommend against the use of SNB in pregnant patients.

Sentinel node biopsy in multicentric and multifocal breast cancer

Multicentric and multifocal diseases have been a relative contra indication to SNB in the past. Some recent studies of SNB with multifocal and multicentric tumours have shown effectiveness. Tousimis and colleagues (99) retrospectively studied patients with multicentric and multifocal tumours who underwent SNB and reported 96% accuracy with a false negative rate of 8%.They recommend SNB for multifocal and multicentric tumours that are smaller than 5cm. ASCO guidelines 2014 states that SNB may be performed for multifocal and multicentric tumours and a sub areolar or intradermal injection is the preferred method

Sentinel node biopsy for in breast tumour recurrence

Patients treated with breast conservation surgery and SNB may have ipsilateral in breast tumour recurrence. Taback and colleagues studied 15 patients with in breast tumour recurrence patients with SNB (100)After breast conservation surgery radio colloid migration time was longer and the drainage was more variable compared with primary breast cancer. Repeat sentinel node biopsy is becoming more frequently employed and further study is indicated, including the optimal interval before repeat sentinel node biopsy should be attempted.(101) Preoperative lymphoscintigraphy should be done if SNB is planned, as these patients often have alternate drainage patterns.

Sentinel node biopsy in inflammatory breast cancer.

Insufficient data exist regarding the use of SNB in inflammatory breast cancer. It is likely that the procedure would not be successful as the dermal lymphatics will be infiltrated with tumour emboli SNB should not be performed in patients with inflammatory breast cancer it is one of the absolute contra indication for SNB.

Sentinel node biopsy after previous axillary surgery

Sentinel node biopsy may fail when the previous operation has removed more than 10 nodes.(102)

SLN MAPPING OF NONAXILLARY NODES

SLN procedures can identify non axillary metastases in up to 43% of cases depending upon the primary tumour location and size, volume of the colloid injected and injection technique(103).Whether this is useful or not is controversial since majority of the published data regarding treatment and outcomes were from evaluation of axillary nodes.

-Internal mammary nodes

Internal mammary (IM) nodes are commonly found in medial tumours more than 2cm size with a rate of 21%. (104).In 8-10% of the patients with axillary lymph nodes IM node will be found.. The diagnosis of positive IM nodes may affect the treatment decisions regarding adjuvant chemotherapy and regional node irradiation. There are limitations to the SLN technique for the identification of IM nodes. Interference with the radioactivity at the primary tumour site will not permit reliable identification of IM nodes(105) Non-invasive methods for IM nodes may be helpful including PET or MRI.The IM nodes are difficult to sample surgically, as separate incision will be required in case of breast conservation surgery and can be complicated by pneumothorax, pleural effusion or bleeding.

The surgical management of positive IM nodes remain controversial There is no consensus on the need of IM nodal dissection with the detection of SLNs. In the absence of definitive data, dissection of the IM nodes with the SLB should be considered investigational .

-Intra mammary node

Intra mammary nodes are present in 1 to 28% of the breast cancer patients. By definition, intra mammary lymph nodes are surrounded by breast tissue and should be distinguished from low axillary lymph nodes. If the intra mammary nodes contain tumour they have the same prognostic significance as a positive axillary lymph nodes with respect to staging(106).ALND should be considered for women with positive intra mammary node even if the axilla is clinically negative because of the high rate of axillary lymph node involvement in these patients(107).

AIM OF THE STUDY*:*

1. To study the feasibility of localization of the sentinel node with the blue dye
2. Compare the nodal tumor positivity in relation to blue dye positivity
3. To analyze whether blue dye technique can be used alone to avoid complete axillary dissection

MATERIALS AND METHODS

Study design:

This **prospective study** was carried out in Department of Surgical Oncology with collaboration of Department of pathology , Government Royepettah Hospital, Chennai. Patients of breast cancer with clinically negative axilla or Patients who had preoperative treatment (chemotherapy and /or RT) and became clinically negative axillae, irrespective of initial axillary nodal status were included in the study, after obtaining informed consent. Thirty five patients with breast cancers with stages T1-T3, N0, and one patient with T3 N1 M0 disease who had become node negative post chemo therapy were included in the study.5 patients with breast cancer clinically node negative axilla were excluded from the study after they have found to have axillary nodes after ultrasound examination. Totally 36 patients were evaluated.

1.Study period: September 2012 to January 2015

2.Inclusion Criteria:

a.Patients with carcinoma breast with clinically negative axillary nodes.

b.Patients who had preoperative treatment (chemotherapy and /or RT) and now have clinically negative axillae, irrespective of initial axillary nodal status.

c.Patients above 18 yrs age with ability to give consent.

3.Exclusion criteria:

a. Clinically palpable axillary nodes

b.Prior upper limb lymphoedema

c.Prior breast / axillary surgery

d.History of blue dye allergy

e.Patients taking serotonergic drugs like paroxetine, fluoxetine etc

METHODS:

Clinical Evaluation:

Comprehensive history was taken and thorough clinical examination was done.

Symptoms were elaborated in detail. Side, T stage of the tumor and type of tumor was noted. Axilla was examined for palpable lymph nodes. Only patients who were clinically negative for lymph nodes at the initial presentation or became clinically node after neoadjuvant chemotherapy were taken in the study.

Ultrasound Examination*:*

Ultrasound examination of the axilla was done with real time scanner with probe head of 7.5 MHz frequency transducer.

Axillary lymph nodes were reported at the time of examination as abnormal on the basis of size criteria and morphology (short-axis diameter > 10 mm, cortical thickening, and lobulation or loss of the normal hyper echoic hilum). If any patient was found to have axillary lymph nodes with the above mentioned features on ultra sonogram they were excluded from the study. Thus 5 patients were excluded.

Sentinel lymph node biopsy (SLNB):

In all selected patients Modified Radical Mastectomy(MRM) was done with an axilla first approach. After induction of anesthesia, peritumoral injection of 1% Methylene blue dye (4ml) at the 3, 6, 9, 12 o'clock positions was done. Sentinel lymph nodes were looked for after raising the superior flap and opening the clavipectoral fascia, within 15 minutes from the time of injection. The stained nodes were removed initially and sent for histopathological examination. Modified radical mastectomy was completed along with axillary lymph node dissection in all cases. The excised breast with the axillary tissue was sent for histopathological examination to correlate with the findings of the sentinel lymph node biopsy

Post operative Histopathology:

Primary tumor:

Post operative specimen of primary tumor was examined under hematoxylin and eosin stain after preparing paraffin sections . Tumor Grade, margin, tumor thickness, vascular invasion, Lymphatic invasion and pathological T stage were noted.

Lymph nodes of axilla:

Number of nodes harvested at each level and nodes positive for blue dye were separately noted. Lymph nodes were bisectioned along the long axis and each lymph node half was examined after fixing and staining.

For both blue dye and non blue dye nodes, the following features were analyzed separately

number of nodes harvested and level of nodes

number of nodes positive for tumor deposits and presenting with features like extra capsular spread and lympho-vascular invasion

ANALYSIS AND RESULTS

The blue node positivity was analyzed with the histopathological findings of the axillary lymph node dissection and the findings correlated with other features such as

Site of primary

Size of the primary

Use of pre operative treatment

Pre operative stage

Pre operative pathological features

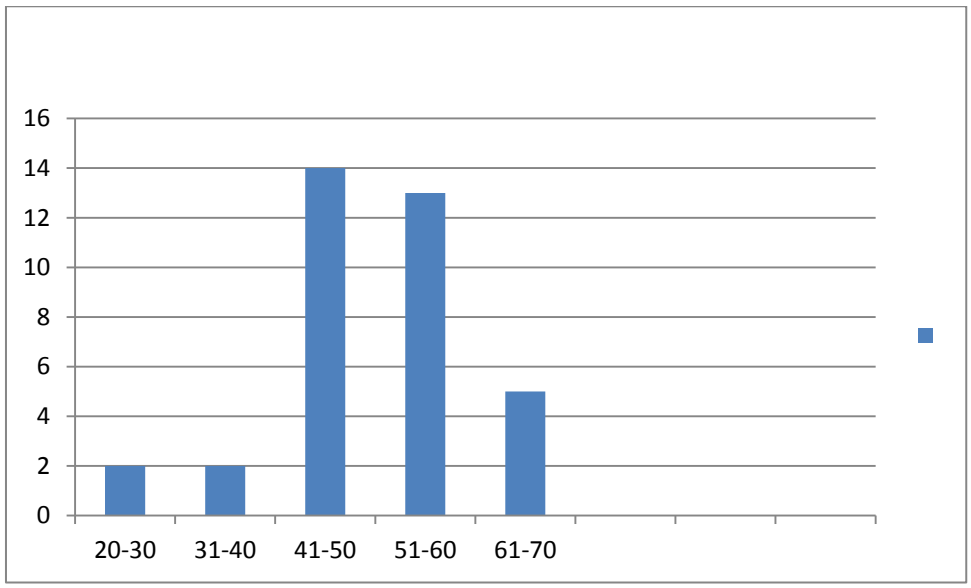
The primary aim of the study was to analyze the feasibility of sentinel lymph node localization in clinically Node negative patients using blue dye. The secondary aims were to identify the prevalence and level of involvement of lymph nodes in carcinoma breast and to correlate it with tumour stage and grade, comparison of accuracy of staging with SLNB to axillary dissection, to identify factors predicting the node positivity in breast cancers and to analyze whether blue dye technique can be used alone to avoid complete axillary dissection.

Statistical analysis was done with Statistical Package for the Social Sciences (SPSS) (version 17.0 software, USA). Quantitative data are described as mean and standard deviations. Data were also presented graphically with bar diagrams and pie charts. Data were explored for any outliers, typing errors and missing values. Comparison of groups was carried out for various categorical variables using Chi-square test of association and Univariate logistic regression analysis to find out any statistical association between categorical variables. The mean values of age and other quantitative variables analysed using one way ANOVA A p-value (two-tailed) < 0.05 was taken as significant.

Age Distribution

In this study 36 patients were evaluated, with mean age of 51 years, and age range was 26-70 years. Incidence was most common in the age group of 41-50 {14/36(38.8%)} cases, followed by 51-60 years{13/36(36.1%)}cases.

FIGURE-3



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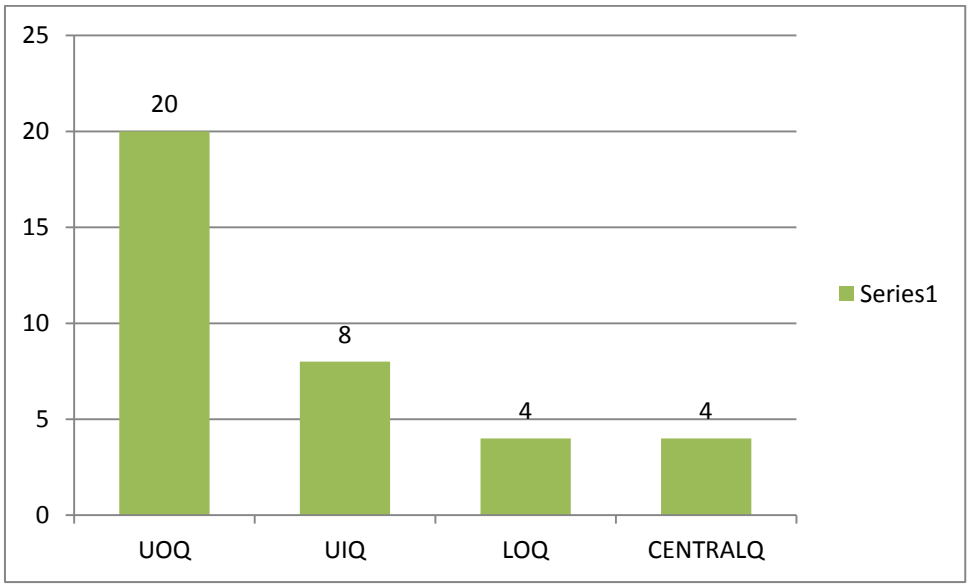
Breast cancer Site Wise - Distribution

In our series left sided lesions19/36{52.7%} were predominant over right sided lesions 17/36{47.3%}. The most commonly involved site was Upper Outer Quadrant (20/36) followed by Upper Inner Quadrant (8/36), Lower Outer Quadrant (4/36), and Central quadrant(4/36) respectively

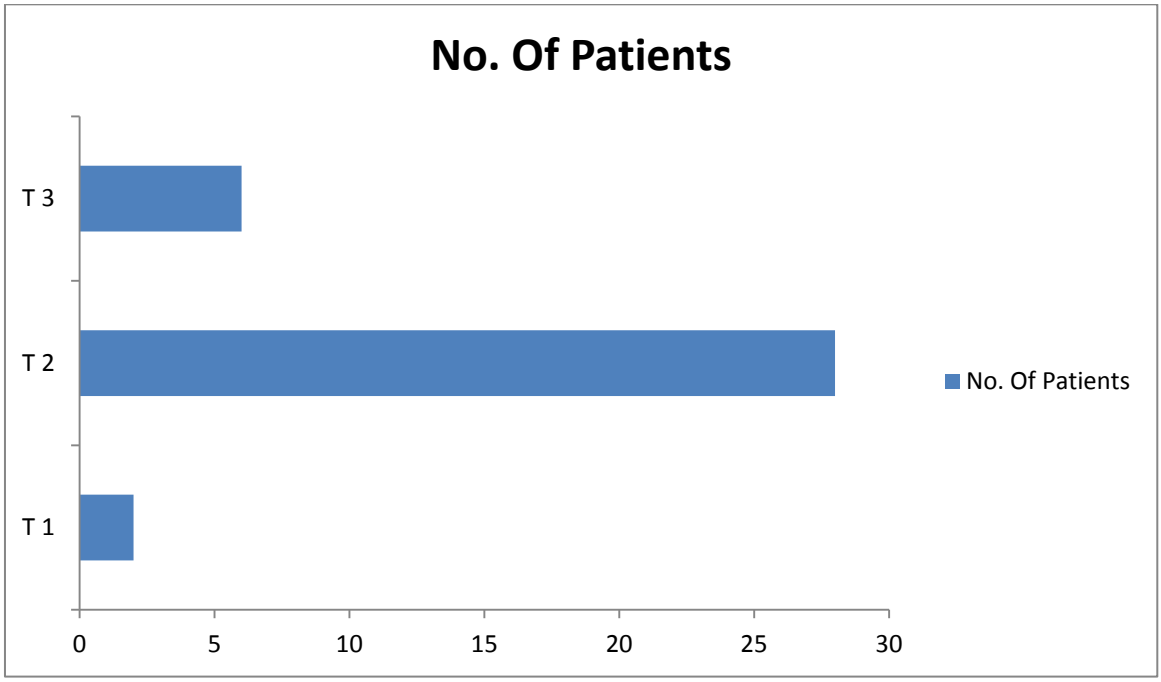
FIGURE-4.



T- Stage Distribution

T Stage distribution includes T 1- 2/36(5.56%) , T 2 – 28/36 (77.78%) , T3 –6/36(16.67 %)

FIGURE-5



General Characteristics

TABLE-5

General Patient characteristics:		No. of patients	Percentage
Age distribution 26-70 (mean 43 years)	Less than 50 years	18	50
	50 years & above	18	50
Side	Left	19	52.8
	Right	17	47.2
Size	T1	2	5.56
	T2	28	77.78
	T3	6	16.67
Site	UOQ	20	55.55
	UIQ	8	22.22
	CENTRAL	4	11.11
	LOQ	4	11.11

Grade	1	8	22.22
	2	19	52.8
	3	9	25

Sentinel node was successfully identified in 32 cases.32/36(88.89%).Among the 32 cases there was skip metastases to level II node in one patient.SLN was not identified in 4 cases 4/36 (11.11%).

There was only one patient with node negative axilla post neoadjuvant chemotherapy. In that patient sentinel node was identified.

Sentinel node identification rate

TABLE-6

Sentinel node	Frequency	Percentage
Identifified	32	88.89
Not identified	4	11.11
Total	36	100

TABLE-7 - Histopathology of the sentinel lymph node

Histopathology of the sentinel lymph node	Frequency	Percentage
Positive	16	50
Negative	16	50
Total	32	100

Sentinel node histopathology positivity VS rest of axillary lymph node histo pathology positivity.

TABLE-8- Comparison of histopathology sentinel node & Rest of axilla

Histopathology of the sentinel lymph node	Histo pathology of the rest of the axillary node			P value
	Positive	Negative	Total	
Positive	2	14	16	0.5442
Negative	1	15	16	
Total	3	29	32	

SENSITIVITY - 2/ 3 = 66.67%

SPECIFICITY - 15/29 = 51.72%

PPV - 2/16 = 12.5%

NPV - 15/16 = 93.75 %

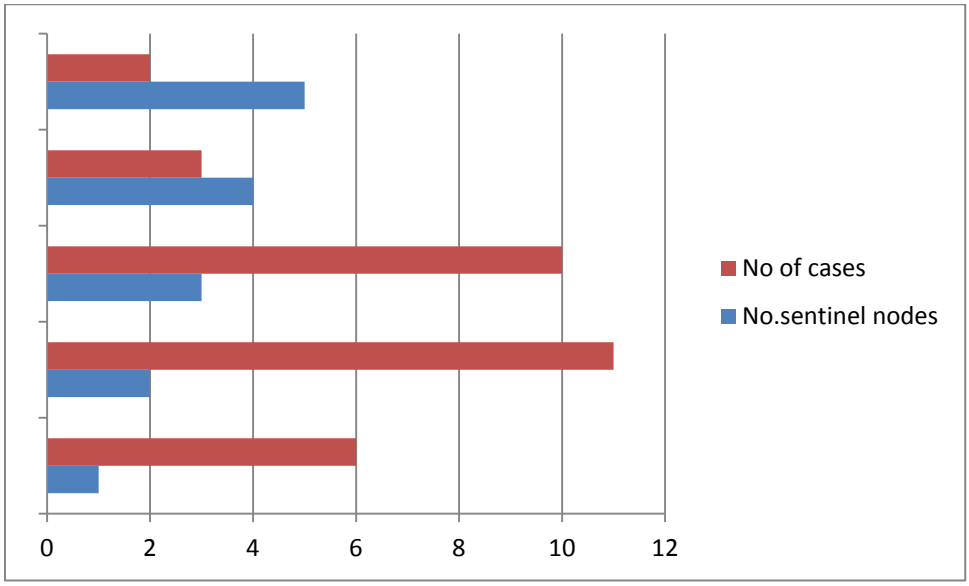
When the histopathological status of axillary lymph nodes was compared to Sentinel lymph nodes histopathology it was seen that when sentinel node HPE was positive(16/32) cases the rest of the axilla was positive in 3 cases and negative in 13 cases and when the sentinel node HPE was negative (16/32) cases the rest of the axilla was also negative in 15 cases except one case . The sensitivity, specificity, positive predictive value and negative predictive values were 66.67%, 51.5%, 12.5% and 93.75% respectively.

In the present study we have dissected 867 axillary lymph nodes and total no of blue nodes harvested 80 and non blue nodes 787. Average sentinel node harvest was 2.22.

TABLE-9

No.sentinel nodes	No of cases
1	6
2	11
3	10
4	3
5	2

FIGURE-6



Factors affecting sentinel node identification

TABLE-10

General Patient Characteristics		Sentinel node - Identified	Sentinel Node -Not identified	Total	P value
Age	<5o	17	1	18	0.6
	>50	15	3	18	
Side	Right	16	3	19	
	Left	16	1	17	0.7

Site	UOQ	19	1	20	
	UIO	7	1	8	
	CEN	3	1	4	
	LOQ	3	1	4	0.3
Size	T1	1	1	2	
	T2	25	3	28	
	T3	6	0	6	0.2
Grade	1	8	0	8	
	2	17	2	19	
	3	7	2	9	0.0

Sentinel node histopathology positive cases

When analyzing the factors affecting the nodal positivity, we found that <50years of age,56.25% ,left sided 43.75% upper outer quadrant 37.5%.grade 2 ,62.5% were associated with sentinel node histopathology positivity but none of these factors except the Grade were statistically significant. Lower the Grade higher was the sentinel node identification rate.

TABLE-9

Patient		No. of	Percentage
Age	<5o yrs	9	56.25
	>50 yrs	7	43.75
Side	Right	9	56.25
	Left	7	43.75
Site	UOQ	8	50
	UIO	4	25
	CENTRAL	2	12.5
	LOQ	2	12.5
Size	T1	0	0
	T2	12	75
	T3	4	25`
Grade	1	5	31.25
	2	10	62.5
	3	1	6.25

DISCUSSION

The status of axillary lymph node remains the most important predictor of survival in women with invasive breast cancer and this is used for making treatment decision. Various methods of predicting axillary lymph node status has been described including clinical assessment, radiological and operative procedures. Axillary lymph node dissection was earlier considered to be the gold standard for predicting the axillary lymph node status. Axillary lymph node dissection may be associated with significant morbidity such as post-operative pain in arm, chronic lymphedema of involved arm, neuropathy of arm, seroma formation, restricted shoulder mobility and other complications. Sentinel Lymph node biopsy has emerged as an effective diagnostic tool in staging axillary disease. The major advantage of Sentinel lymph node biopsy is the lower complication rate compared with Axillary lymph node dissection

The present study was conducted to assess the feasibility of sentinel lymph node localization using methylene blue dye alone.

36 patients were included whose axilla was clinically negative for lymphadenopathy. 35 patients were subjected to primary surgery and one patient was treated with neoadjuvant chemotherapy and subsequently became node negative. Although number of patients included was small (N= 36) it was comparable to studies done by Krag et al(l08)(N=22) Borgstein et al(109)(N=33), Pijpiers et al(110)(N=34), Ikeda et al(111)(N=29) ,Motta C et al(112)(N=54), Seenu and Bassi et al(l13)(N=40) .

36 patients were evaluated with a median age of 51 and the study group was similar to what is reported in literature.Sentinel node identification was higher in the age group of <50 years. Patient age was inversely correlated with the ability to identify the SLN. This finding has been reported previously and may be related to the inability of the blue dye to be taken up by the lymphatic system when injected into the fat-replaced postmenopausal breast Altan Özdemir et al(114) studied 32 patients with a median age 0f 50.Arindam Mukherjee et al(115) evaluated 27 patients with a median age of 43.

In this study both right and left side were more or less equally affected with slight predominance of left sided lesions(19/36). Upper outer quadrant was involved in (20/36)55.6% of cases followed by upper inner quadrant (8/36)22.2%,central quadrant((4/36)11% and lower outer quadrant.(4/36).sentinel node was identified readily in the upper outer quadrant tumors 95% followed by upper inner, central and lower outer quadrant locations with similar identification rate of 75%

Right side (72%) and upper outer quadrant(75%) were the most common side and site of tumor location in a study by Altan Ozdemir-et al.2013 In the study by Arindham Mukherjee et al upper outer quadrant 44% was the most common site of tumor

Clinical tumor status include T1 (2/36) 5.6%,T2(28/36) 77.8% and T3(6/36)16.7% and gradeI-I- (8/36)-22.2%,gradeII-(19/36)52.8% grade-III(9/36)25% with highest sentinel node identification in T3 & Grade I lesions about 100%

. In this study clinical characteristics did not affect sentinel node identification except Tumor Grade and it is similar to the results observed by Kollias et al(116) who studied clinical and histological factors associated with sentinel node identification

Either isosulphane blue or methylene blue can be used as a dye in sentinel lymph node biopsy. Methylene blue is cheaper, more easily obtainable, and is a dye with fewer complications as compared to isosulphane blue. Hypersensitivity reactions which may also be fatal are reported at a rate of 0.6 to 2.5 % following isosulphane blue injection. Skin necrosis, if injected intradermally ,fat necrosis, and fibrosis over the injection site are among complications of methylene blue. However, in the present study, no such complications related to methylene blue was encountered. In studies conducted in our country isosulphane blue was often preferred . In the literature, there are many studies showing that methylene blue can be used safely and with high success as an alternative to isosulphane blue . Simmons and colleagues have identified the sentinel lymph node in 104 of 112 patients by using methylene blue and reported that sentinel lymph node represented axillary status in 96.9% of patients. Bleesing et al. compared isosulphane blue and

methylene blue, and found the accuracy rate as 88.5 % with isosulphane blue and as 92.7% with methylene blue.

In this study also sentinel node identification with blue dye alone was 88.88%.In comparision other studies have reported sentinel node identification, with methylene blue dye alone , ranging from 65-94%(Blessing *et al.*Simmons *et al.*Nour - Golshan (117), *et al.* 2006) , slightly improved rates with combination of both radioactive colloid and blue dye(94%100%).

In the present study, we dissected 867 axillary lymph nodes from 36 patients and subjected for histopathological examination for evidence of metastasis. We could identify 80 blue stained sentinel lymph node during the procedure with average of 2.2 sentinel node This finding is in conjunction with identification rates of several authors like Giuliano et al10(1.8), Motomura K etal26(1.8),Cserni et al25(1.3)Cox et al20(1.92), Hill etal21(2.1),Ikeda et al07(1.95), Albertini et al11(2) (118)Increasing the mean number of SNs removed may improve accuracy.

Sentinel lymph nodes identification with combination/blue dye alone methods

TABLE-10

Study/Author	No. of Cases	SN Identification Rate (%)	FN Rate (%)
Canavese (2009)	202	97.1	6.5
Krag (1998)	443	91.0	11.0
Tafra (2001)	529	87.0	13.0
SNAC [19]	1,080	94.5	5.5
NSABP-B32	5,611	97.1	9.8
ALMANAC	803	96.1	6.7
ACOSOG Z010	5,283	98.7	0.3
Sentinella/GIVOM	697	95.0	6.7
Rama maniet al2014(119)	96	72%	14.5

Study/Author	No. of Cases	SN Identification Rate (%)	FN Rate (%)
Altan Özdemir et al	`32	94	15
This study	36	88	6.25

In this study of 36 cases, the sentinel lymph node detection rate was over 88.8% and the negative predictive value was 93.75%. The rate of false-negative result best defines the accuracy of Sentinel lymph node biopsy. In this study, false-negative result was seen in one patient. (6.25%). This is comparable with those of other published studies by Blessing *et al.*Simmons *et al.*Nour - Golshan (22), *et al.* 2006)

Only one patient was post neoadjuvant chemo therapy in this study. She initially had T3 N1M0 disease and became node negative after 3 cycles of neo adjuvant chemotherapy with 5 flurouracil, adriamycin and cyclophophamide(y c T3N0M0) .In that patient we could identify the sentinel node and could accurately predict the axillary status, as both sentinel nodes and rest of the axillary nodes were positive for malignancy.

Our results indicate that SLNB can reliably predict the axilla status such that when sentinel node is negative for metastases, axillary dissection can be safely omitted.

A recent survey on SLNB distributed by American Society of Breast Diseases Rapid Response Panel demonstrates that SLNB is considered to be the standard of care by 85% of the members who responded. It has been suggested that surgeons should demonstrate an SLN identification rate of more than or equal to 90% and a false negative rate of less than 5% before they offer SLNB without completion axillary dissection.(120) However, before

SLNB becomes the undisputed standard of care, randomized trials will have to show no difference in axillary recurrence and overall survival (OS) between SLNB alone and SLNB followed by axillary dissection in patients with negative sentinel node(s). Blue dye along with Tc99m mapping theoretically increases the accuracy of test but from various validation studies it is clear that blue dye technique alone can be used when Tc99m mapping facility is not available.

Pitfalls of this study:

1.Need for the flap raising to identify sentinel lymph node within 15 to 20 minutes because the dye transit time is rapid and blue staining of distal, non-sentinel axillary LNs is not uncommon

2.Small number of patients

3. Exposure of the entire axilla before visual identification of blue sentinel node.

Conclusions:

1. This study demonstrates that sentinel node localization is possible with methylene blue dye alone.

2. Though limited by small sample size this study has shown a low false negative rate of 6.25%. which denotes that SLN biopsy using methylene blue dye alone is a highly reliable and predictable technique to stage the axilla in breast cancer patients. This technique may help to avoid complete axillary lymph node dissection in sentinel node negative patients thereby minimising the morbidity of axillary lymph node dissection.

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118) **Predictability and Reliability of Sentinel Lymph Node Biopsy in Women with EarlyBreast Cancer using patent blue dye"**

1Dr Padmanabh Inamdar , 2Dr Garima Mehta , 3Dr Jayapraksh J Kashalikar, 4Dr Dhanashree Deshpande International J. of Healthcare & Biomedical Research, Volume: 1, Issue: 3, April 2013, Pages 150-1

119)Sentinel Lymph Node Biopsy For Breast Cancer Using Methylene Blue

Dr.Rama mani.L Dr.Manohar pai, Dr. U. Anand kini.

Surgery, KMC Mangalore,MANIPAL UNIVERSITY/INDIA

Sentinel lymphnode biopsy in early breast cancer using

methylene blue dye and radioactive sulphur colloid – a single

institution Indian experience S. P. Somashekhar . S. Zaveri Shabber . K. Udupa Venkatesh . K. Venkatachala . Parameshwaran .

M. M. Vasan Thirumalai Indian J. Surg. (May–June 2008

PROFORMA

NAME
CD No.
ADDRESS

AGE / SEX
I.P. No.

PHONE No.

OCCUPATION:

COMPLAINTS:

1. Lump – Mode of onset
   Duration
   Rate of growth
   Ulcer
2. discharge from the nipple
3. swelling in axilla/neck
4. pain
5. retraction of nipple
6. others

HISTORY:

- H/O loss of weight/appetite
- Past h/o similar swelling
- h/o cough, dyspnea, hemoptysis
- h/o jaundice, abdominal pain
- h/o headache, fits, vomiting
- h/o bony pain
- others

MENSTRUAL HISTORY:

- Age at menarche
- Cycle period
- Last month period
- Age at menopause

MARITAL HISTORY:

- consanguinity

OBSTETRIC HISTORY:

- Number of children
- Age at first child birth
- Feeding habits
- Abortion
- Oral Contraceptives
- HRT

PERSONAL HISTORY:

- Smoking
- Alcohol
- Diet

PAST HISTORY:

- H/O co morbid illness

- Surgery
- Prior malignancy
- Prior radiation

FAMILY HISTORY

TREATMENT HISTORY

GENERAL EXAMINATION

PS
Nutritional status
Anaemia
Jaundice
Pedal edema

Pulse / BP
Height
Weight
BSA
BMI

LOCAL EXAMINATION:
Primary tumor:

Side: Left
Right

Lump: Nil
Definite - single multiple
Vague

Size

Site UOQ/UIQ/CENTRAL/LOQ/LIQ

Consistency
Soft
Cystic
Firm
Hard

Nipple/Areola
Paget's
Nipple retraction
Nipple discharge

Skin
Edema
Ulceration
Satellite nodule
Peau d orange

Edema of arm

Fixation
Nil
Pectoralis major
Chest wall

Opposite breast

Lymph nodes (Prior the Chemo / Radiotherapy)

		Number	Mobile	Fixed
Axillary	Ipsilateral			
	Contra lateral			
Supraclavicular				
	Ipsilateral			
	Contra lateral			

Gynaec examination

INVESTIGATIONS

Hemoglobin

TC, DC, ESR

Blood sugar

Blood urea

S.creatinine

LFT

Mammogram/USG Breast / USG Axilla

FNAC/Bx

Date No. Lab.

HPE

Date No. Lab.

FINAL DIAGNOSIS:

STAGE:

TREATMENT POLICY:

CHEMOTHERAPY - Neoadjuvant

REGIMEN

No. OF CYCLES

RADIOTHERAPY - Neoadjuvant

SURGERY DATE

Type of surgery Modified radical mastectomy

1. No. of lymph nodes – Taken up the Dye - ☐

Level	I	II	III
	☐	☐	☐

2. Total No. of lymph nodes dissected - ☐

Level	I	II	III
	☐	☐	☐

Lymph node histopathalogy	No. of Nodes Dye Positive	No. of Nodes Dye Negative
Positive		
Negative		

Follow-up

1. Recurrence
   - Loco regional
   - Lymph node
   - distant

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.12117/ME-1/Ethics/2012 Dt:03.01.2013.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on assessment of sentinel nodes with methylene blue dye in carcinoma breast" for dissertation purpose submitted by Dr.J.Sakthi Usha devi, MCh (Surgical Oncology), PG Student, Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

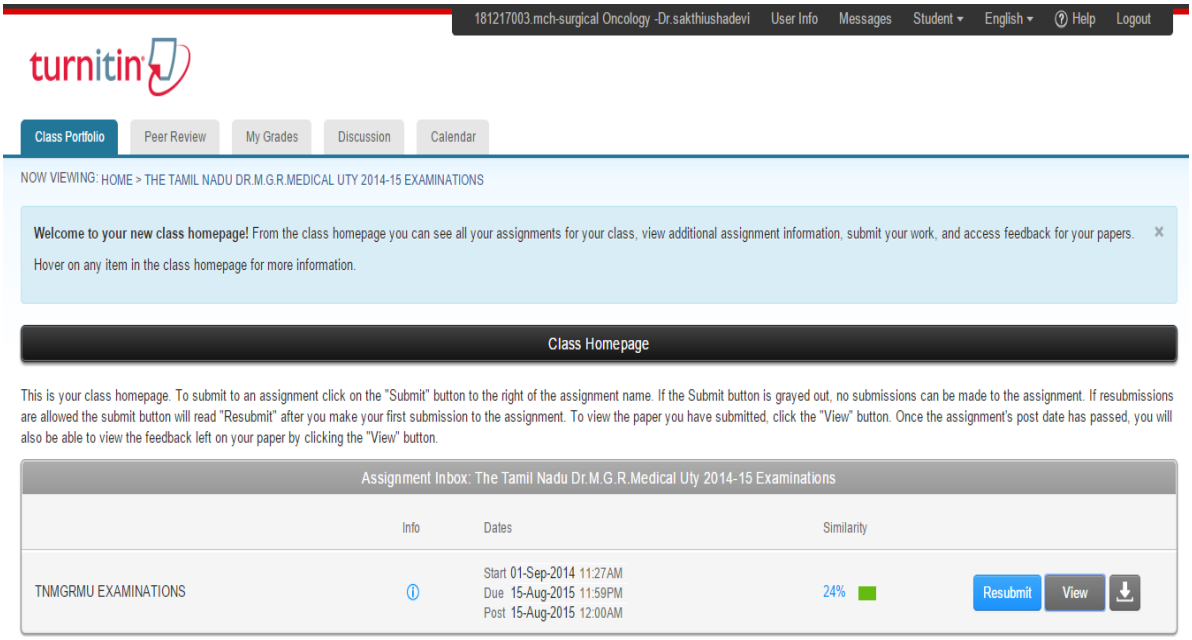
21/1/13

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

Blue node identified during the operative procedure

Blue stained node along with perilymphatic fat

Modified radical mastectomy specimen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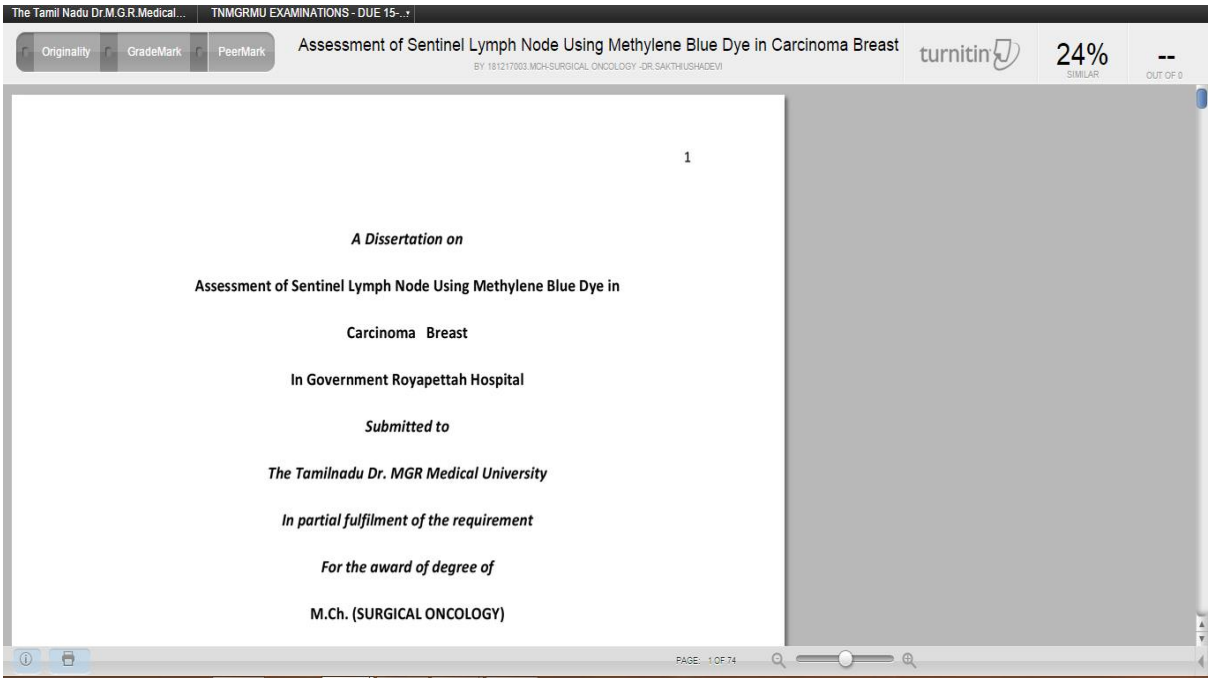
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In Government Royapettah Hospital
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The Tamilnadu Dr. MGR Medical University
In partial fulfilment of the requirement
For the award of degree of
M.Ch. (SURGICAL ONCOLOGY)
PAGE: 1 OF 74

S. No.	NAME	AGE/SEX	CD NO	SIDE	SITE	STAGE	T	N	M	GRADE	HPE	BN L I	BN L II	BN L III	NBN L I	NBN L II	NBN L III	BN+ROA+	BN+ROA-	BN-ROA-	BN-ROA+	NACT
1	MALLIGA BEGUM	61/F	1356/13	LEFT	CEN	IA	T1	N0	M0	3	IDC	0	0	0	22	1	1	0	0	22	0	NO
2	KARPAGAVALLI	44/F	453/13	LEFT	UOQ	IIA	T2	N0	M0	2	IDC	2	0	0	12	2	1	0	2	18	0	NO
3	YASODHA	53/F	1140/14	LEFT	UOQ	IIA	T2	N0	M0	3	IDC	2	0	0	13	1	1	0	2	13	0	NO
4	THULASI	58/F	683/13	LEFT	UIQ	IIA	T2	N0	M0	2	IDC	0	0	0	14	3	2	0	0	19	0	NO
5	VALARMATHY	50/F	208/15	LEFT	UOQ	IIA	T2	N0	M0	2	IDC	0	0	0	14	0	1	0	2	16	0	NO
6	KARPAGAM	48/F	606/13	LEFT	UIQ	IIA	T2	N0	M0	2	IDC	2	0	0	16	3	2	0	2	19	0	NO
7	LAKSHMI	54/F	790/13	LEFT	UOQ	IIA	T2	N0	M0	2	IDC	3	0	0	16	2	2	0	3	20	0	NO
8	AMUDHAVALLI	47/F	1241/14	lEFT	UOQ	IIA	T2	N0	M0	1	IDC	1	0	0	18	2	2	0	1	22	0	NO
9	GNANAMANI	69/F	119/13	LEFT	UIQ	IIA	T2	N0	M0	3	IDC	1	0	0	20	2	3	0	1	25	0	NO
10	MALLIGA	57/F	309/15	LEFT	UOQ	IIA	T2	N0	MO	1	IDC	2	0	0	22	1	0	0	2	22	0	NO
11	SHANTHI	45/F	783/13	RIGHT	UOQ	IIA	T2	N0	M0	2	IDC	1	0	0	11	1	1	0	1	13	0	NO
12	SUGUNA	54/F	1203/14	RIGHT	UOQ	IIA	T2	N0	M0	2	IDC	3	0	0	11	0	0	0	3	10	1	NO
13	VANAJA	46/F	244/13	RIGHT	LOQ	IIA	T2	N0	M0	2	IDC	1	0	0	12	4	2	0	1	18	0	NO
14	RAJESWARI	63/F	118/13	RIGHT	UOQ	IIA	T2	N0	M0	2	IDC	2	0	0	14	4	2	0	2	20	0	NO
15	SAHAYARANI	40/F	725/13	RIGHT	UOQ	IIA	T2	N0	M0	2	IDC	3	0	0	14	2	2	0	4	12	0	NO
16	RAJESWARI	55/F	504/13	RIGHT	CEN	IIA	T2	N0	M0	3	IDC	3	0	0	16	2	1	0	0	19	1	NO
17	ANTHONY AACHI	60/F	1568/14	RIGHT	LOQ	IIA	T2	N0	M0	3	IDC	0	0	0	16	0	0	0	3	13	0	NO
18	MAHMOODHA BEE	49/F	1279/13	RIGHT	UOQ	IIA	T2	N0	M0	3	IDC	2	0	0	21	1	1	0	2	24	0	NO
19	JAGADEESWARI	30/F	177/13	LEFT	UOQ	IIB	T3	N0	M0	3	IDC	3	0	0	14	3	4	0	3	21	0	NO
20	VICTORIA	50/F	1142/13	RIGHT	UOQ	IIB	T3	N0	M0	3	IDC	3	0	0	18	2	2	0	3	22	0	NO
21	Nagarathinam	63/F	1240/13	LEFT	UIQ	IIA	TI	N0	MO	1	IDC	2	0	0	17	2	2	0	0	21	0	NO
22	ANSARI BEGUM	55/F	835/13	LEFT	LOQ	IIA	T2	N0	M0	1	IDC	1	0	0	13	1	2	1	0	14	1	NO
23	GEETHA	39/F	985/13	RIGHT	UIQ	IIA	T2	N0	M0	2	IDC	0	1	0	16	2	2	1	0	15	4	NO
24	PADMAVATHY	47/F	1327/13	RIGHT	UOQ	IIA	T2	N0	M0	1	IDC	2	0	0	18	2	1	1	1	21	0	NO
25	SARASWATHY	60/F	674/13	LEFT	UIQ	IIB	T3	N0	M0	2	IDC	3	0	0	14	2	2	1	2	18	0	NO
26	BANUMATHY	56/F	1194/12	RIGHT	UOQ	IIIA	T3	NI	M0	2	IDC	2	0	0	18	4	2	1	1	23	1	YES
27	VIJAYA	50/F	1153/12	LEFT	UOQ	IIA	T2	N0	M0	3	IDC	2	0	0	14	4	2	2	0	20	0	NO
28	KUDRATH BEE	60/F	1650/14	RIGHT	CEN	IIA	T2	N0	M0	1	IDC	3	0	0	12	2	2	2	1	14	2	NO
29	SAKUNTHALA	60/F	1709/14	RIGHT	CEN	IIA	T2	N0	M0	1	IDC	3	0	0	12	2	1	2	1	15	0	NO
30	KASIAMMAL	70/F	643/14	RIGHT	UIQ	IIA	T2	N0	M0	2	IDC	5	0	0	20	1	0	2	3	21	0	NO

31	KALAIARASI	48/F	1044/13	RIGHT	UOQ	IIA	T2	N0	M0	1	IDC	4	0	0	21	3	3	2	2	24	3	NO
32	RAJESWARI	46/F	504/14	LEFT	UIQ	IIB	T3	N0	M0	2	IDC	2	0	0	14	1	0	2	0	15	0	NO
33	SUDHA	26/F	347/13	RIGHT	UOQ	IIB	T3	N0	M0	2	IDC	3	1	0	15	6	3	2	2	24	0	NO
34	RANI	55/F	1336/13	LEFT	UOQ	IIA	T2	N0	M0	2	IDC	4	0	0	14	1	1	3	1	16	0	NO
35	JAYA	43/F	1226/13	LEFT	LOQ	IIA	T2	N0	M0	2	IDC	3	0	0	14	2	2	3	0	14	0	NO
36	PADMINI	50/F	1360/13	LEFT	UOQ	IIA	T2	N0	M0	2	IDC	5	0	0	17	2	2	4	1	20	1	NO

Abbreviations for Master Chart

1. CD No - Cancer Department number
2. UOQ - Upper Outer Quadrant
3. UIQ - Upper Inner Quadrant
4. CEN - Central
5. LOQ - Lower Outer Quadrant
6. IDC - Infiltrating Ductal Cacinoma
7. BN - Blue Dye Stained Nodes
8. NBN - Non Blue Dye Stained Nodes
9. HPE - Histopathological Examination
10. NACT - Neoadjuvant Chemotherapy
11. BN+ROA+ - HPE of Blue Node Positive & Rest of Axilla Positive
12. BN+ROA- - HPE of Blue Node Positive & Rest of Axilla Negative
13. BN-ROA+ - HPE of Blue Node Negative & Rest of Axilla Positive
14. BN-ROA- - HPE of Blue Node Negative & Rest of Axilla Negative